American Journal of Medical Genetics 63:80–83 (1996)

An Unknown Spondylo-Meta-Epiphyseal Dysplasia in Sibs With Extreme Short Stature

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In three sibs of Jordanian descent a unique type of severe spondylo-meta-epiphyseal dysplasia results in extreme disproportionate dwarfism. They have a distinct facial appearance with hypotelorism, prognathia, and hypodontia. The limbs are short and the hands and feet stubby. Radiologically, the irregular end plates of the vertebral bodies, the very small and late appearing epiphyseal ossification centres, and the hypoplastic acetabular roofs are most impressive. Histopathologic studies of the growth plate demonstrate characteristic findings with fingerprint-like inclusion bodies in the hypertrophic chondrocytes. This seems to be a distinct, autosomal recessive skeletal dysplasia.

KEY WORDS: spondylo-meta-epiphyseal dysplasia, extreme short stature, histopathology, autosomal recessive

INTRODUCTION

Most skeletal dysplasias lead to short stature, but adult height rarely is less than 100 cm. Here we describe a skeletal dysplasia in sibs with extreme short stature.

FAMILY HISTORY AND CLINICAL REPORTS

The family originates from Jordan; family history is unremarkable. The parents are first cousins, healthy, and of normal height. Twelve children were born to this couple, three sisters and one brother are similarly affected. One affected sister also had Fanconi anemia and died at the age of 8 years in Jordan. One 7-year-old sister also has Fanconi anemia without skeletal dysplasia. The diagnosis of Fanconi anemia was confirmed by the increased rate of chromosome breakage in lymphocytes after treatment with diepoxybutane (Prof. Dr. T. Schroeder-Kurth, Heidelberg, Germany). One boy with esophageal atresia, VSD, and dysmelia died shortly after birth. One brother and three sisters are healthy and of normal height.

The four affected sibs were born spontaneously after uneventful, term pregnancies. Birth weight, length, and head circumferences were below the 3rd centile. At birth, short stature with short limbs was obvious.

The three affected living sibs were admitted to our hospital for examination of short stature. They were 19, 7, and 3 years old and, respectively, 85, 69, and 66 cm tall. On clinical examination, they had a rather uniform

Fig. 1. The three affected sibs at 19, 7, and 3 years together with their father.

Received for publication January 12, 1996; revision received January 16, 1996.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

appearance (Fig. 1) with hypotelorism, prognathia, and normal palate. All primary teeth were present in the two younger sibs but were small. In the 19-year-old girl, all permanent maxillary teeth were present, whereas the mandibular incisors and cuspids were absent. All sibs had a short neck, barrel chest, and lumbar hyperlordosis. The oldest sister also had a marked kyphoscoliosis. There was rhizomelic shortness of the limbs with stubby hands and feet. The large joints were prominent and the oldest sister had limited extension at the elbows. They had rocker bottom feet with prominent heels. Genitalia appeared normal and the pubertal development of the oldest sister was normal for age. Vision and hearing were normal. All were slightly mentally retarded (Fig. 2).

Laboratory studies showed normal values of Ca, P, alkaline phosphatase, BUN, vitamin D3, and urinary mucopolysaccharides.

RADIOGRAPHS

Radiographs of the skull showed mid-face hypoplasia and a steep base of the skull with an enlarged, J-shaped sella. The vertebral bodies had a concave posterior surface and were oval shaped in the youngest sib and foreshortened in the oldest (Fig. 3). The lateral aspect of the iliac bodies were hypoplastic with slanting acetabular roofs; the pubic bones were gracile. The femoral heads were very small and became deformed in the older sibs; no femoral necks were visible (Fig. 4). All tubular bones were severely short with irregular metaphyses and small and deformed epiphyses. The carpal bones appeared late. The phalanges were short and broad and the terminal phalanges hypoplastic (Fig. 5).

HISTOLOGIC FINDINGS

An iliac crest biopsy was performed in the 7-year-old girl. Light microscopy was performed on paraformaldehyde fixed, undecalcified sections. For electron microscopy, the specimens were fixed in 4% paraformaldehyde containing ruthenium red. Light microscopy showed a severely distorted growth plate, greatly reduced in size with only a few disseminated chondrocytes. Columnization of the hypertrophic zone

Fig. 2. The 19-year-old patient. The face is mildly unusual with hypotelorism and prognathia. Short neck, scoliosis, short limbs with stubby hands and feet are noticeable.

Fig. 3. Lateral view of the spine in the 7-year-old patient. The end plates are irregular, the posterior margins concave.

Fig. 4. Pelvis of all three patients. **a–c:** The lateral aspect of the iliac bodies is hypoplastic with slanting acetabular roofs, the pubic bones gracile. The femoral heads are very small and show deformities in the older sibs; the femoral necks are not visible. **c:** In the oldest sister the left femoral neck was dislocated.

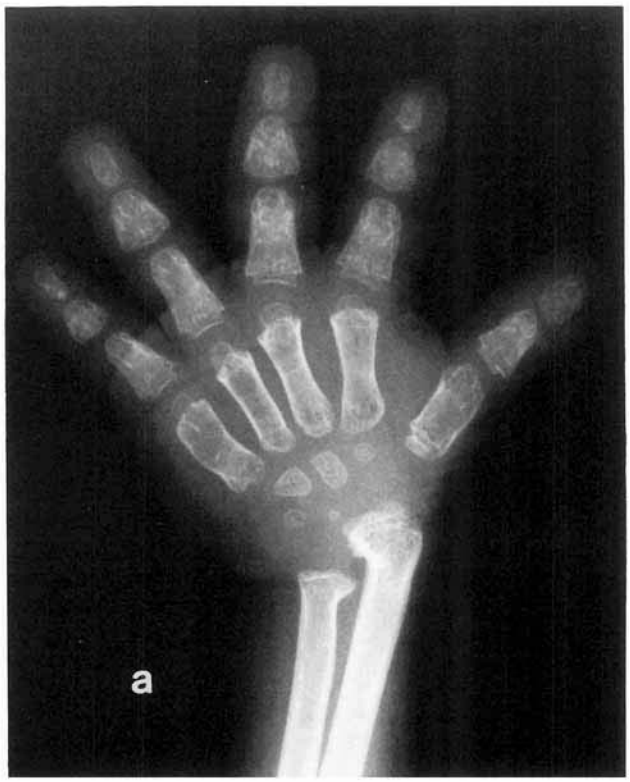

Fig. 5. Hands of the 3- and the 7-year-old patients. **a,b:** The ulna is distally short. The carpal bones appeared late and were very small. The phalanges seem to be short and broad and the end phalanges hypoplastic.

was nearly absent and the osteochondral junction was highly irregular. Mineralisation was patchy and the bone trabeculae were reduced in size and number (Fig. 6).

Ultrastructurally, the remaining hypertrophic chondrocytes showed a dilated rough endoplasmic reticulum containing granulated material in the form of fingerprint-like profiles of alternating layers of electron-lucent and electron-dense material in some cells. In some of them the inclusion bodies were very large and the cells appeared degenerated (Fig. 7). The collagen fibrils in the surrounding cartilage matrix seemed smaller and less numerous than normal but showed no major abnormality.

Light microscopy of a skin biopsy of the same patient presented a normal architecture. Arrangement, periodicity, and bundle size of collagen fibres were ultrastructurally normal.

DISCUSSION

In this sibship born to normal but consanguineous parents, two autosomal recessive disorders segregate independently. One is the subject of this discussion. The other, Fanconi anemia, was confirmed in one of the affected girls by the typical cytogenetic result of increased chromosome breakage. Another son may have had the VACTERL association, but details were unknown.

The growth retardation leads to a height of less than 90 cm in the oldest and adult daughter. This extreme degree of shortness is known in only a few skeletal dysplasias including the different types of microcephalic osteodysplastic primordial dwarfism [Herman et al., 1991; Meinecke et al., 1991] and other conditions [Young et al., 1985]. Distinction between these disorders and the cases presented in this report is possible, on clinical and radiological grounds. Radiologically, our patients differ from other rare spondylo-meta-epiphyseal dysplasias [Shebib et al., 1991].

The relatively mild metaphyseal abnormalities have their histological reflection in a growth plate reduced in size with nearly absent columnization. Late-appearing and small epiphyses correspond to the marked hypocellularity of all parts of the growth plate including the resting cartilage. Thus, the cause of this disorder apparently affects the chondrocytes in all growth plate areas.

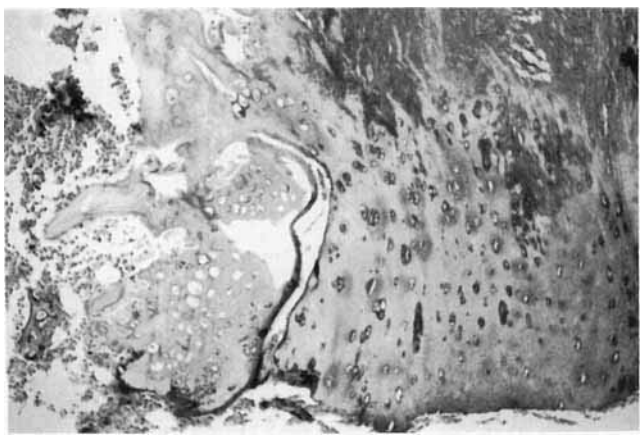

Fig. 6. Light microscopy of the iliac crest growth plate in the 7-year-old patient. The growth plate is severely distorted with only few disseminated chondrocytes. There is almost no columnization and the osteochondral junction is highly irregular.

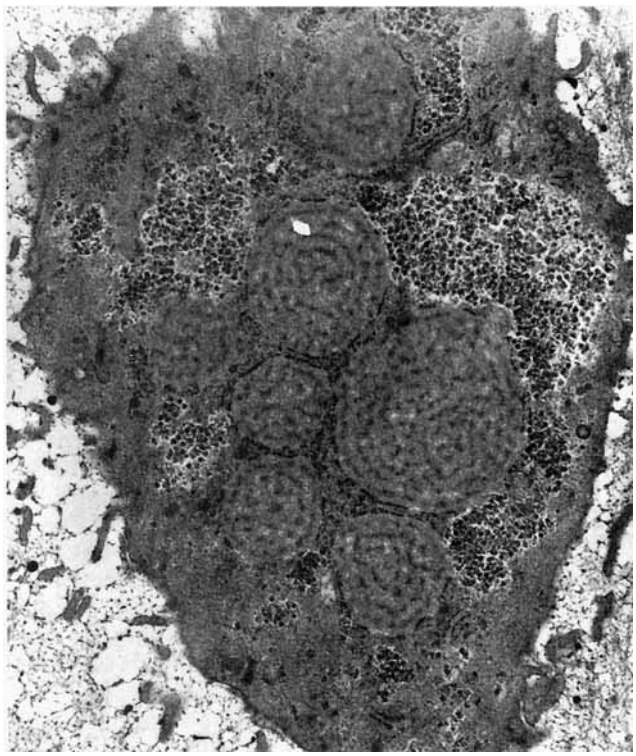

Fig. 7. Electron microscopy of a chondrocyte of the hypertrophic zone of the iliac crest growth plate in the 7-year-old patient. The rough endoplasmatic reticulum contains granulated material with fingerprint-like profiles. These inclusions consist of alternating layers of electron-lucent and electron-dense material arranged in snail-like whorls.

The large intracellular inclusion bodies with fingerprint-like structures partly resemble those found in pseudoachondroplasia [Stanescu et al., 1984]. However, their appearance is different as they do not resemble variegated whorls and are found only in some cells close to the osteochondral junction.

In conclusion, we report an unique chondrodysplasia with only few hints to etiology and pathogenesis. Molecular studies, using this family for linkage analysis to test candidate genes, will be the first step towards the identification of a gene so essential for normal growth and skeletal development.

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